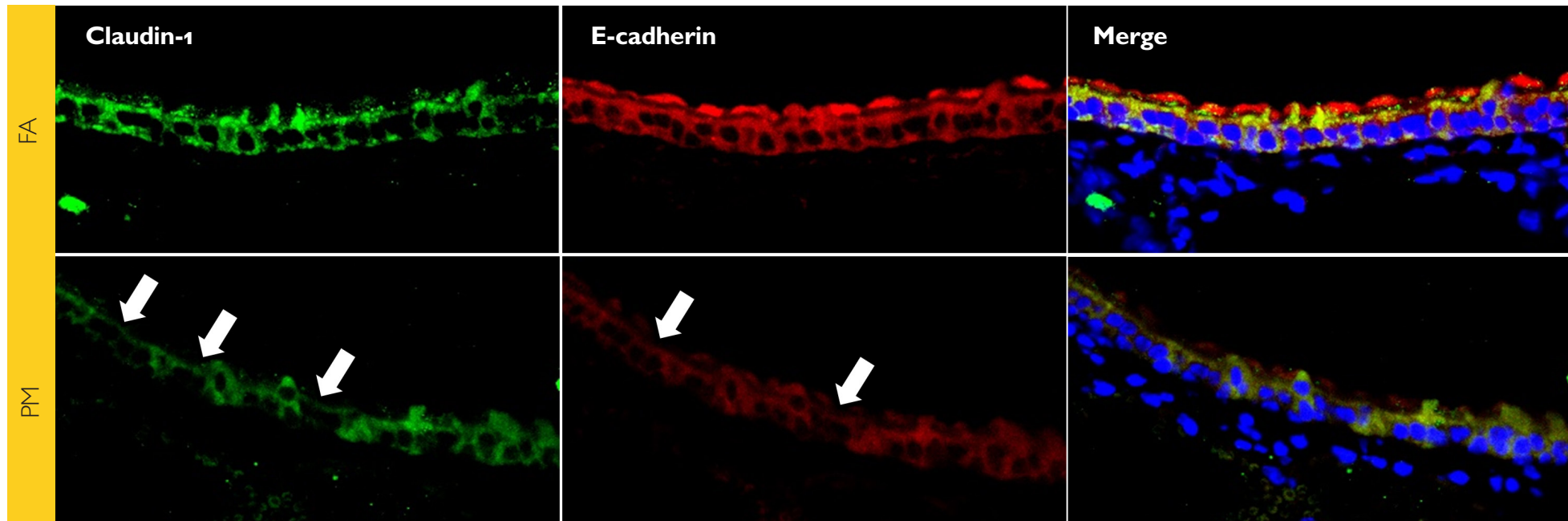


# HeadWay

NEWS FOR PHYSICIANS FROM JOHNS HOPKINS OTOLARYNGOLOGY-HEAD AND NECK SURGERY



## Air Pollution's Link to Chronic Sinusitis

Although human population studies have linked air pollution to chronic inflammation of nasal and sinus tissues, direct biological and molecular evidence for cause and effect has been scant. Now, research in mice, led by Johns Hopkins otolaryngologist-head and neck surgeon **Murugappan Ramanathan**, suggests that continual exposure to dirty air can lead to a bevy of consequences that mimic human chronic sinusitis—a condition that affects more than 29 million individuals in the U.S.

The new findings, Ramanathan says, have broad implications for the health and well-being of people who live in large cities and industrial areas with polluted air, particularly in the developing world.

“In the U.S., regulations have kept a lot of air pollution in check, but in places like New Delhi, Cairo or Beijing, where people heat their houses with wood-burning stoves, and factories release pollutants into the air, our study suggests people are at higher risk of developing chronic sinus problems,” he explains.

To see how pollution may directly affect the biology of the upper airways, the researchers exposed 38 eight-week-old male mice to either filtered air or concentrated Baltimore air with particles measuring 2.5 micrometers or less, which excludes most allergens, like dust and pollen. The aerosolized particles, although concentrated, were 30 to 60 percent lower than the

average concentrations of particles of a similar size in cities like New Delhi, Cairo and Beijing.

Nineteen mice breathed in filtered air, and 19 breathed polluted air for 6 hours per day, 5 days a week for 16 weeks.

After flushing the noses and sinuses of the mice with water and examining the resulting fluid under a microscope, the researchers saw significantly more white blood cells that signal inflammation, including macrophages, neutrophils and eosinophils, in the mice that breathed in the polluted air compared with those that breathed in filtered air. The elevated neutrophils and eosinophils seen in the sinonasal mucosa of mice exposed to polluted air is very similar to the profile that chronic rhinosinusitis patients exhibit in Asian countries suffering from air pollution.

Further investigation found elevated levels of direct biomarkers for inflammation such as interleukin 1b, interleukin 13, oncostatin M and eotaxin-1. Other signs of inflammation included a thicker epithelium and lower levels of proteins that hold epithelial cells together.

Ramanathan says his team will continue to study the upper respiratory changes that occur after exposure to pollution, as well as potential ways to reverse them. For example, he says, it's not yet known whether removing the pollutant—or the individual from a polluted environment—can reverse any pollutant-

*(continued on back cover)*

Chronic airborne particulate matter (PM) exposure in mice causes a breakdown (white arrows) in sinonasal epithelial junctional proteins, claudin-1 (green left column) and e-cadherin (middle red column) when compared to mice exposed to filtered air (FA) as measured by immunofluorescence and confocal microscopy. This breakdown may allow for increased susceptibility to other allergens, viruses or bacteria.

“SOMEDAY WE MAY HAVE A DRUG THAT COULD COMPLETELY REVERSE THIS CONDITION IN OUR PATIENTS.”

—MURUGAPPAN RAMANATHAN



RESEARCH

# Offering Hope for Genetic Hearing Loss

Gene therapy in mouse model of Usher syndrome partially restored hearing.

**U**sher syndrome—the rare genetic disorder that’s the world’s leading cause of deafness-blindness—occurs in three different forms. In the most severe one, children are born deaf with vestibular problems and develop vision problems early in life. There’s no cure, and no good treatments beyond cochlear implants, an imperfect solution compared to restoring native hearing.

However, research in an animal model, led by Johns Hopkins neuro-otologist **Wade Chien**, could be the starting point for the first treatment for this condition that helps restore natural hearing for this and other genetic forms of deafness as well.

ALTHOUGH WILD-TYPE MICE WITH NO WHIRLIN MUTATION CAN TYPICALLY HEAR SOUNDS AS LOW AS 30 DECIBELS, BEING ABLE TO PARTIALLY RESTORE HEARING IN THIS MOUSE MODEL IS A TREMENDOUS ADVANCE.



Wade Chien

Chien and his team worked with mice that had a recessive mutation in the whirlin gene, a known cause of some cases of Usher syndrome. This mutation renders the hair-like extensions on inner ear sensory cells (hair cells) short and dysfunctional. Thus, these animals are deaf and tend to spin in circles rather than walk in a straight line.

In a recent study, Chien and his colleagues injected a viral vector carrying normal whirlin cDNA into the inner ears of these whirlin mutant mice. Within weeks, mice that received whirlin gene therapy were able to walk in straight lines and produced robust auditory brainstem responses to sounds as low as 60-70 decibels—about the volume of a normal human conversation. This response lasted at least four months in most of these animals.

Although wild-type mice with no whirlin mutation can typically hear sounds as low as 30 decibels, being able to partially restore hearing in this mouse model is a tremendous advance, Chien says. The finding shows that gene therapy has potential for treating Usher

syndrome and potentially other forms of hearing loss caused by genetic mutations as well.

Applying gene therapy to these conditions still faces some significant hurdles before it can be available to human patients, Chien explains. Researchers will need to show that this therapy is safe and effective for humans, and they’ll need to better understand how early it needs to be applied to be effective. Ideally, he says, tweaks in the protocol will help improve hearing even in adults.

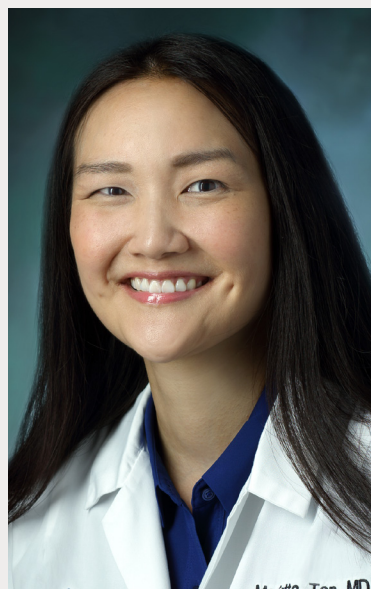
“The last major breakthrough that we had for hearing loss was the cochlear implant, which was developed in the 1960s, so we’ve gone through half a century now without any major innovation in therapies,” Chien says. “This is something that we think has a lot of promise for Usher and other genetic hearing disorders.” ■

To refer a patient, call 443-997-6467

HEAD AND NECK SURGERY



Vaninder Dhillon



Marietta Tan

## New Faculty Members

Two new faculty members recently joined the Johns Hopkins Department of Otolaryngology-Head and Neck Surgery.

**Vaninder Dhillon, M.D.**, treats patients with thyroid diseases, parathyroid diseases, benign and malignant diseases of thyroid and parathyroid, voice, swallowing and airway problems. Her dual fellowship training in endocrine surgery and laryngology allows her to care for both thyroid and parathyroid patients, as well as laryngology patients. Dhillon sees patients at the Johns Hopkins Health Care and Surgical Center in Bethesda, Maryland. Her research interests include voice outcomes in thyroid and parathyroid patients, neurogenic vocal cord immobility (vocal cord paralysis)

and prognosis, and ablation techniques for thyroid nodules.

**Marietta Tan, M.D.**, is a head and neck cancer surgeon specializing in the treatment of benign and malignant tumors of the head and neck, including the upper aerodigestive tract, salivary glands, thyroid and parathyroid glands, and skin. Tan sees patients at the Johns Hopkins Bayview Medical Center. Her research efforts have focused on the molecular biology and molecular genetics underlying the development of head and neck cancer. ■

To refer a patient, call 443-997-6467

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# Better Understanding **Ankyloglossia**

Increasing tongue- and lip-tie diagnoses are drawing scrutiny from Johns Hopkins doctors.

Several years ago, Johns Hopkins pediatric otolaryngologist–head and neck surgeon **Jonathan Walsh** noticed a trend: More and more infant patients were being referred to his practice for ankyloglossia, colloquially known as tongue-tie. These abnormal attachments of the lingual frenum can restrict the tongue’s movement, potentially hampering the complex and coordinated interactions between mother and baby necessary for successful breastfeeding.

In a relatively recent culture where “breast is best,” increasing breastfeeding rates in the U.S., it makes sense that more babies might be diagnosed with breastfeeding problems that might have been overlooked in bottle-feeders. But, is tongue-tie being overdiagnosed? And are the procedures used to remedy this problem—such as in-office clipping or laser frenotomy—always necessary?

Walsh and his Hopkins colleagues who evaluate and treat ankyloglossia and the related condition known as lip-tie, including **David Tunkel**, **Emily Boss**, and **Margaret Skinner**, decided to investigate this problem. In a recent paper authored by Walsh, Tunkel and Boss, the researchers put numbers to the tongue-tie diagnosis trend.

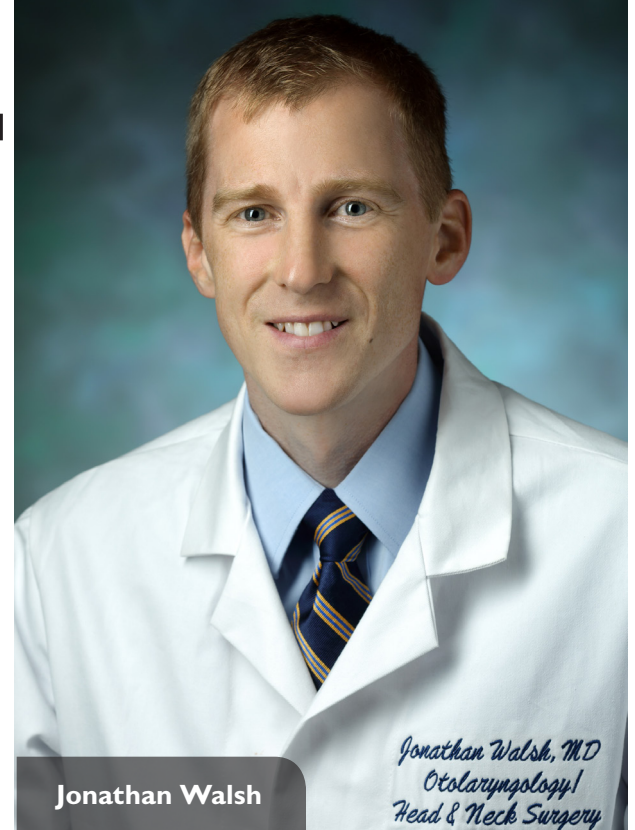
Using a national database with discharge information on millions of patients from thousands of American hospitals, the researchers searched for billing codes related to ankyloglossia from 1997 to 2012. Their search turned up steady increases over the years, from a mere 3,934 cases diagnosed in 1997 to nearly 33,000 diagnosed in 2012. Similarly, frenotomy increased with

1279 procedures in 1997 to more than 12,000 in 2012.

Although it’s clear these rates have increased substantially over the years, it’s unclear exactly why. Increased rates of breastfeeding are likely a factor, Walsh says, but data from their recent study and others have shown that ankyloglossia is more frequently diagnosed in the babies of first-time parents who are privately insured and in relatively high-income areas, suggesting that societal expectation and health disparities could be factors.

To get more insight on tongue-tie diagnosis and treatment decisions, Walsh and his colleagues have embarked on a study that’s examining social media and open blogs to analyze emerging trends on what parents are expressing about this condition. They’re also analyzing the available web-based information on tongue-tie to determine whether the resources that parents often turn to—such as WebMD or eMedicineHealth—adhere to evidence-based medicine and recommended reading levels for information geared toward nonexperts.

Lastly, Walsh points out that a lingering issue with both tongue- and lip-tie is that what constitutes a real pathology deserving treatment is unknown—there’s a wide variation of lingual and maxillary frenum anatomy, and it’s what’s in the range of normal. To help answer this question, he and his colleagues are conducting an ongoing study of lip-ties that involves taking photos of the maxillary frenum of every infant whose parents consent in Johns Hopkins’ healthy newborn nursery. Using image analysis, they’re gathering information on the



Jonathan Walsh

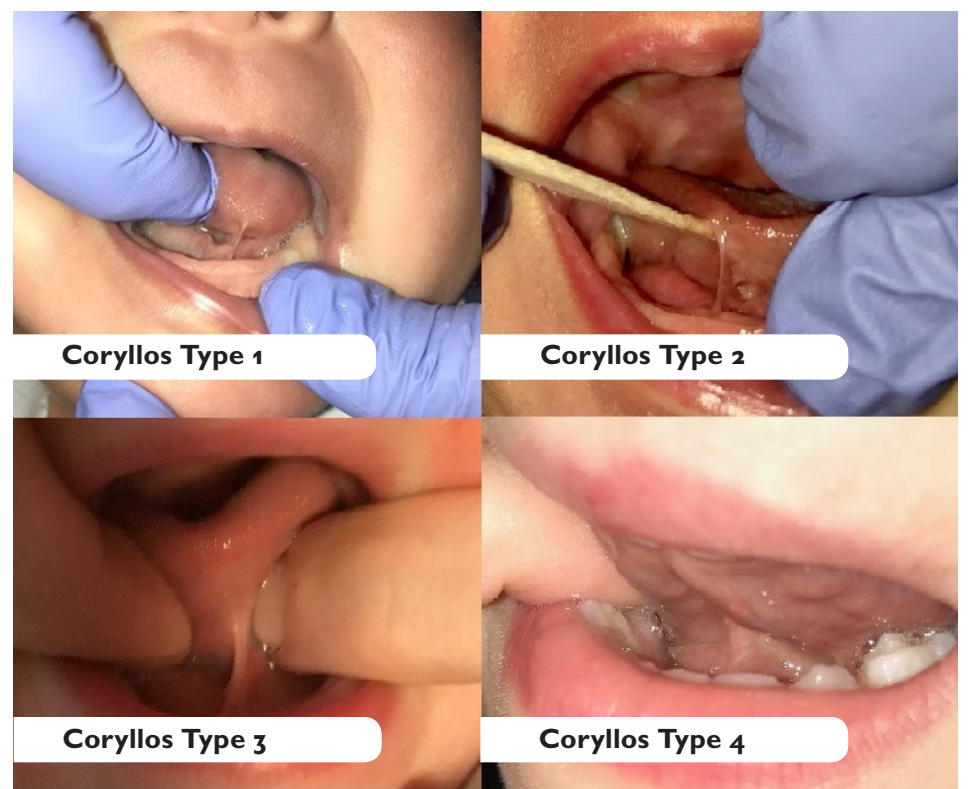
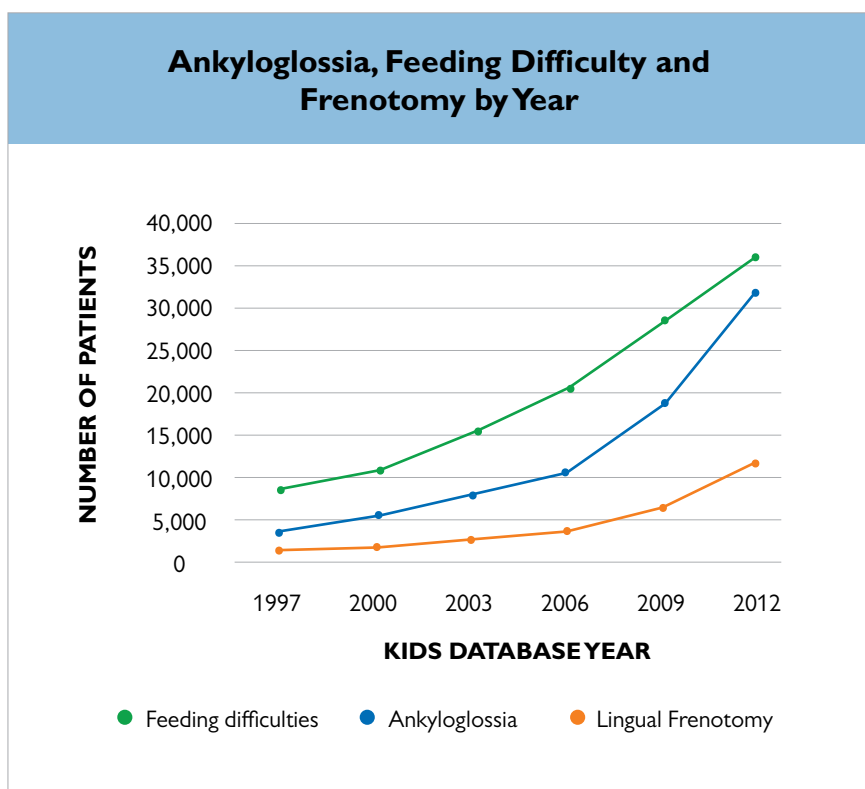
*Jonathan Walsh, MD  
Otolaryngology/  
Head & Neck Surgery*

frenum length, attachment, morphology and other clinical characteristics—including whether the baby has difficulty breastfeeding—to determine what constitutes a problem that needs treating.

“Until we figure out how best to diagnose which children are really having problems, we’ll be doing procedures on many more children than will be helped,” Walsh says. “We’re hoping to clarify which children will truly benefit from these interventions.” ■

To refer a patient, call 443-997-6467

Coryllos Ankyloglossia grading scale



Please include the following patient information:

- Name
- Date of birth
- Medical problem
- Patient’s contact information
- Physician office contact information

## Air Pollution's Link to Chronic Sinusitis

(continued from front cover)

related damage.

The findings also suggest some molecular pathways that could serve as targets for prophylactic or therapeutic interventions that could prevent or treat chronic sinusitis caused by fine particulates.

“Someday,” he says, “we may have a drug that could completely reverse this condition in our patients.” ■

To refer a patient, call 443-997-6467



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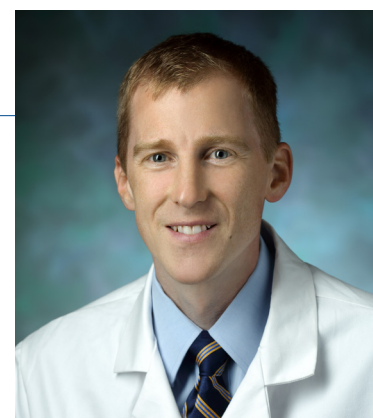
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**Better  
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